Regulatory Considerations for Biomarker Development – Analytical and Clinical Validation of IVDs

FDA Public Workshop - Advancing the Development of Biomarkers in Traumatic Brain Injury

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What is an IVD?

"Reagents instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae in man. … for use in the collection, preparation, and examination of specimens from the human body." [21 CFR 809.3]

Used in clinical laboratories & other settings
(e.g., Point-of-Care/Over-the-Counter)

What is an IVD?

In Vitro Diagnostic Tests for :

- Diagnosis
- Screening
- Prediction
- Prognosis
- Epidemiology/Surveillance
- First Response

- **Not** Environmental Screening

Intended Use

As for other devices, IVD review is driven by the intended use of the device

The risk of an IVD is based on the consequences of a false result

The type of review [510(k), PMA, etc.] and the types of validation studies that are needed depend on the claims that are made in the intended use

Intended Use

The Intended Use is the driving force of the review:

The Astute Medical NEPHROCHECK® Test System is intended to be used in conjunction with clinical evaluation in patients who currently have or have had within the past 24 hours acute cardiovascular and or respiratory compromise and are ICU patients as an aid in the risk assessment for moderate or severe acute kidney injury (AKI) within 12 hours of patient assessment.

The NEPHROCHECK® Test System is intended to be used in patients 21 years of age or older.

Premarket Review

All IVDs must establish adequate:

Analytical performance

- How accurately does the test measure the analyte?
- How reliably?
- Limit of Detection, Potential Interferences / Cross-Reactivity, Linearity, Carry-over, etc.

Clinical performance

- How reliably does the test measure the clinical condition?

Labeling (21 CFR 809.10)

- Adequate instructions for use
- Intended use, directions for use, warnings, limitations, interpretation of results, performance summary

Clinical Performance

Clinical validity

- Device must have a clinical indication/clinical validity

Samples/Populations

- Should represent Intended Use population
- May be prospectively collected or based on retrospective studies or literature. If retrospective, should reflect intended use population, investigate sample storage
- Clearly defined inclusion/exclusion criteria
- # of positives statistically appropriate

Example

Novel biomarker test to rule out TBI in at-risk patients

- Retrospective study compares predictive value of biomarker test to outcome (CT scan) for each patient
- Negative predictive value is excellent, everyone is excited

CAUTION:

- Study used banked samples from a study intended to assess a different intended use; only included patients that had CT scan, excluded all others
- Different performance seen when used in whole intended use population
  - Selection bias not controlled for – this design favors patients more likely to have CT scan ordered in this time frame
  - Baseline risk of included vs. excluded patients may not be the same
  - Inclusion/exclusion criteria for this study may not be appropriate for this test
  - PPV and NPV (or even relative risk) cannot be accurately calculated

- May need to devise a study that follows patients that don't get a CT scan

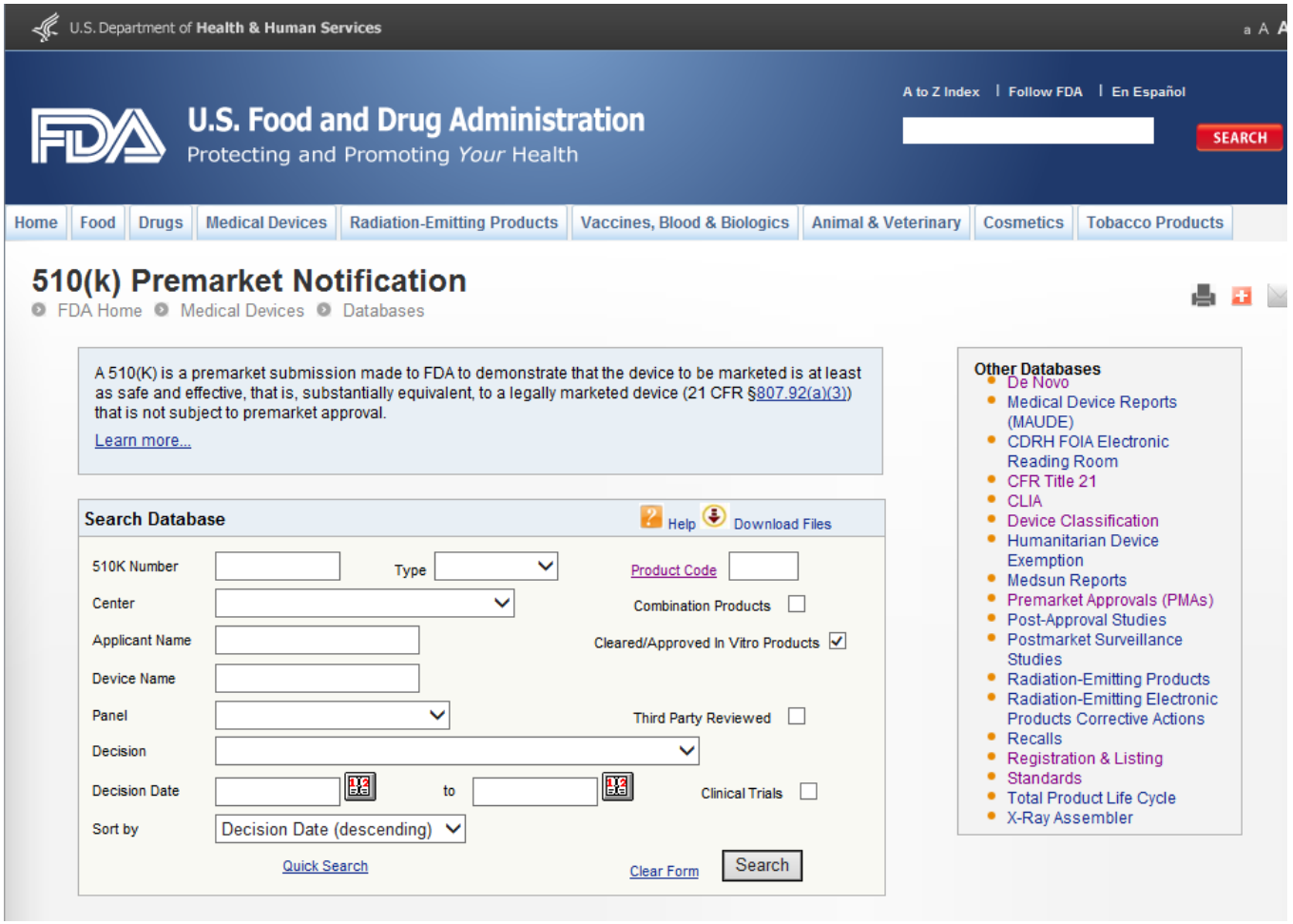
FDA Guidance Documents

- In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions
- Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests
- Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices etc.
- Requests for Feedback on Medical Device Submissions: the Pre-Submission Program and Meetings with Food and Drug Administration Staff

We also recommend the Clinical Laboratory and Standards Institute Evaluation Protocol Guidelines

Transparency

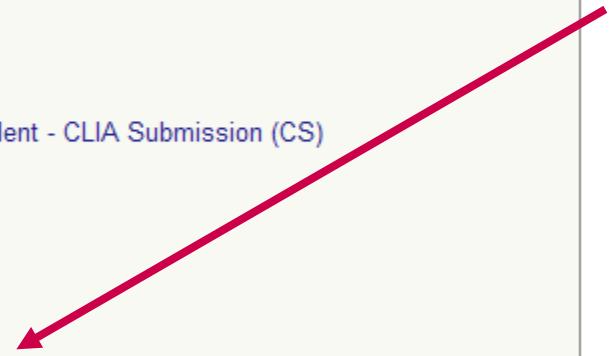
510(k) Database: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm



Transparency

New Search | Back To Search Results

Device Classification Name	System, Test, Amino Acids, Free Carnitines And Acylcarnitines Tandem Mass Spectrometry
510(K) Number	K083130
Device Name	NEOBASE NON-DERIVATIZED MSMS KIT, MODEL 3040
Applicant	PERKINELMER, INC. 8275 Carloway Road Indianapolis, IN 46236
Contact	Kay A Taylor
Regulation Number	862.1055
Classification Product Code	NQL
Date Received	11/13/2008
Decision Date	07/09/2009
Decision	Substantially Equivalent - CLIA Submission (CS)
Classification Advisory Committee	Clinical Chemistry
Review Advisory Committee	Clinical Chemistry
Summary	Summary
FDA Review	Decision Summary
Type	Traditional
Reviewed By Third Party	No
Expedited Review	No



Thank you!

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